Evaluation of acute and late radiation morbidity in patients with gynaecologic malignancy using the RTOG criteria and Franco-Italian glossary

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Summary

Purpose: The purpose of this study was to evaluate acute and late radiation morbidity in patients with gynaecologic malignancy using the RTOG criteria and Franco-Italian glossary, and to compare the usefulness and disadvantages of each system. *Materials and Methods:* Between February 2001 and February 2003, 107 patients with gynaecologic malignancy who received either radical or adjuvant external radiotherapy ± intracavitary brachytherapy or radiochemotherapy were enrolled in this study. The patients were evaluated before radiotherapy and weekly during radiotherapy for acute morbidity using the RTOG grading system and Franco-Italian glossary. Postradiotherapy evaluation was done one month after radiotherapy and at 3-month intervals thereafter. Median follow-up duration was 17 months. Morbidity was graded and recorded according to each scoring system. *Results:* Median age was 46 years (range 37-82). Sixty-four patients (59.8%) had endometrial cancer. Radical radiotherapy was applied to 26 patients because of inoperability and 81 patients received postoperative radiotherapy. Biologically effective doses for the bladder, rectum and vagina were 98.39, 103.54 and 121.81, respectively, for late morbidity (BED_3); 70.88, 72.84 and 80.92, respectively, for acute morbidity (BED_{10}). According to the RTOG grading system acute morbidity rate for the genitourinary and gastrointestinal systems, and skin were 52.3%, 83.2% and 63.5%, respectively. Late morbidity rate for the bladder, colon-rectum, skin and vagina were 16.8%, 20.6%, 47.7% and 51.4%, respectively. The morbidity rate for the bladder, nonspecific abdominal, hematopoietic system, uterus-vulva-vagina, skin and rectum were 35.4%, 29.9%, 5.6%, 60.8%, 40.1% and 32.7%, respectively using the Franco-Italian glossary. In patients with carcinoma of the vulva – whose treatment fields were wider – acute morbidity rate according to RTOG criteria was higher ($p = 0.057$); photon energy (6 Mv rather than 1.25 MV) ($p = 0.01$) and treatment interruption of more than eight days ($p = 0.019$) were correlated with decreased long-term morbidity. According to the Franco-Italian glossary morbidity rates were higher in patients who received chemotherapy ($p = 0.047$), both external radiotherapy and brachytherapy ($p = 0.022$) and treatment interruption of less than eight days ($p = 0.019$). *Conclusion:* There is no common language between the RTOG grading system and Franco-Italian glossary for defining and scoring radiation morbidity. Up to date no standard and well-defined system has been developed for recording and reporting acute and late radiation morbidity in gynaecologic malignancy, but rather it depends on the subjective evaluation and experience of a radiation oncologist and subjective complaints of the patient, and sometimes on clinical findings. A standard and well-defined user friendly objective scoring system is needed to define and predict the morbidity rate more properly.

Key words: Radiation therapy; Collateral effects; RTOG; Franco-Italian glossary.

Introduction

In recent years, survival rates of cancer patients have improved significantly due to the progress in cancer treatment. Therefore postoperative care, rehabilitation, attempts to decrease treatment complications and to improve quality of life have gained importance. From this point of view preservation of normal tissues or organs has become an important aspect of radiotherapy. Although there are various studies reporting acute and late radiation morbidity a uniform toxicity scoring system is still lacking. At present the major national or international toxicity scoring systems include RTOG (Radiation Therapy Oncology Group), EORTC (European Organization for Research and Treatment of Cancer), ECOG (Eastern Cooperative Oncology Group), CCSG (The Crohn's and Colitis Support Group), Franco-Italian Glossary for gynaecologic malignancies and MRC (Medical Research Council) [1-4].

In the present study we evaluated the acute and late effects of treatment in patients with gynaecologic malignancy using the RTOG grading system and Franco-Italian glossary to determine the compatibility and the sufficiency of the two different grading systems.

Materials and Methods

Between February 2001 and February 2003, 107 patients with gynaecologic malignancy who received either radical or adjuvant external radiotherapy (ERT) ± intracavitary brachytherapy (IBRT) or radiochemotherapy were enrolled in this study. Radiotherapy portals were AP/PA pelvic, four-field pelvic box, paraaortic + pelvic or paraaortic + pelvic + inguinal portals depending on the type and the stage of the disease. ERT was delivered with megavoltage beams (Co60 in 27.1% of the patients and 6 MV photon beam in 72.9%) using 1.8 Gy per fraction, five fractions per week. Median total ERT dose was 50.4 Gy in operable patients and 59.4 Gy in inoperable patients (with parametrial boost after 54 Gy). Midline shielding was performed at 50.4 Gy. Two fractions of 6.5 Gy were given to a depth of 7 mm from the vaginal surface in operable patients with the ovoids of the Rotterdam applicator and three fractions

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of 6 Gy with weekly intervals were applied to point A in inoperable patients with the Rotterdam applicator via microSelectron-HDR remote afterloader Ir-192. Weekly cisplatin (40 mg/m^2) was given concurrently with radiotherapy to inoperable or high-risk patients.

The patients were evaluated before radiotherapy and weekly during radiotherapy for acute morbidity using the RTOG criteria and Franco-Italian glossary. Postradiotherapy evaluation was done one month after radiotherapy and at 3-month intervals thereafter.

Statistical analyses were done using the SPSS V. 10.0 computer programme. The Mann-Whitney U test was used for comparison of the median values between independent variables and the Kruskal-Wallis test was used for comparison of the median values in more than two groups. Values of $p \leq 0.05$ were considered statistically significant.

Results

Median age of the patients was 46 (range 37-82). Most of the patients had endometrial carcinoma and most of them were operated on. General characteristics of the patients are shown in Table 1.

Biologically effective doses for early (BED_{10}) and late (BED_3) effects for the bladder, rectum and vagina are indicated in Table 2.

Early morbidity was defined as complications occurring during or within three months after radiotherapy and late morbidity as those complications occurring later than three months. According to the RTOG grading system gastrointestinal toxicity was the most frequent early morbidity (Table 3). Late morbidity is indicated in Table 4.

Toxicity grading according to the Franco-Italian glossary is listed in Table 5.

Table 1. — *General characteristics of the patients.*

	No. of patients	%
Age		
Median 56 (range 37-82)		
Operation type		
TAH+BSO	50	46.7
Wertheim	28	26.2
Simple vulvectomy	3	2.8
Inoperable	26	24.3
Primary tumour type		
Carcinoma of the endometrium	64	59.8
Carcinoma of the uterine cervix	33	30.8
Ovarian cancer	5	4.7
Vulvar cancer	3	2.8
Vaginal carcinoma	1	0.9
Treatment portals		
AP/PA pelvic	65	60.7
Four-field pelvic	24	22.5
Paraaortic + pelvic	10	9.3
Paraaortic + pelvic + inguinal	8	7.5
Brachytherapy		
Yes	79	73.8
No	28	26.2
Chemotherapy		
Yes	29	27.2
No	78	72.8

Table 2. — *BED_{10} and BED_3 values for the bladder, rectum and vagina.*

Organ	Median total dose (Gy)	BED_{10} (Gy)	BED_3 (Gy)
Bladder	58.59	70.88	98.39
Rectum	59.72	72.84	103.54
Vagina	63.40	80.92	121.81

Table 3. — *Acute morbidity according to the RTOG grading system.*

Grade	Gastrointestinal	Genitourinary	Skin
1	17 (15.9%)	27 (25.2%)	35 (32.7%)
2	71 (66.4%)	26 (24.3%)	32 (29.9%)
3	1 (0.9%)	3 (2.8%)	1 (0.9%)
Total	89 (83.2%)	56 (52.3%)	58 (63.5%)

Table 4. — *Late morbidity according to the RTOG grading system.*

Grade	Skin	Subcutaneous tissue	Bladder	Small/large intestine	Mucosa (vaginal)
1	42 (39.3%)	18 (16.8%)	2 (1.9%)	20 (18.7%)	27 (25.2%)
2	8 (7.5%)	11 (10.3%)	14 (10.3%)	2 (1.9%)	16 (15.0%)
3	1 (0.9%)	3 (2.8%)	2 (1.9%)	–	12 (51.4%)
Total	51 (47.7%)	32 (29.9%)	18 (16.8%)	22 (20.6%)	55 (51.4%)

Table 5. — *Toxicity grading according to the Franco-Italian glossary.*

Grade	Bladder	Nonspecific	Hematopoietic abdominal	Uterus-vulva-vagina	Cutaneous tissue	Rectum
1	34 (31.7%)	30 (28%)	1 (0.9%)	34 (31.8%)	39 (36.4%)	31 (29%)
2	1 (0.9%)	2 (1.9%)	–	28 (26.2%)	4 (3.7%)	3 (2.8%)
3	3 (2.8%)	–	5 (4.7%)	3 (2.8%)	–	1 (0.9%)
Total	38 (35.4%)	32 (29.9%)	6 (5.6%)	65 (60.8%)	43 (40.1%)	35 (32.7%)

Potential factors which could influence the toxicity rate included age, diabetes, obesity, prior surgery, total ERT dose, BED_3 and BED_{10}, treatment portals, photon energy, chemotherapy, brachytherapy, and treatment interruption. Parameters such as age ($p = 0.167$), diabetes ($p = 0.589$), obesity ($p = 0.07$), prior surgery ($p = 0.615$), total ERT dose above 50.4 Gy ($p = 0.145$), administration of chemotherapy ($p = 0.772$), application of brachytherapy ($p = 0.159$), the photon energy used-1.25 MV or 6 MV ($p = 0.7$), and treatment interruption more than eight days ($p = 0.979$) had no significant correlation with the development of acute morbidity according to the RTOG system whereas there was a trend with extended treatment fields including paraaortic or inguinal lymph nodes ($p = 0.057$). The significant factors influencing late morbidity rate were the photon energy ($p = 0.01$) and treatment interruption more than eight days ($p = 0.019$) which were correlated with a decreased long-term morbidity rate.

The Franco-Italian system does not categorize morbidity as acute or late, rather it evaluates it more detailed as a whole. Factors such as age ($p = 0.694$), operation type ($p = 0.178$), total ERT dose ($p = 0.967$), the photon energy used ($p = 0.821$), and the treatment portal ($p = 0.488$) had no significant impact on the development of morbidity according to the Franco-Italian glossary.

Administration of chemotherapy (p = 0.047), and brachytherapy application (p = 0.022) increased the morbidity rate while treatment interruption of more than eight days (p = 0.019) decreased it.

Discussion

Although the aim of radiotherapy is to achieve maximum local control with minimum treatment related complications, specific acute and late complications involving different systems and organs in different degrees of frequency and severity can be seen either during or after radiotherapy. Especially late morbidity has a great influence on the patient's quality of life. There are many factors such as total dose, irradiation technique, fractionation and daily dose, use of midline shielding, etc., which influence the likelihood of complications both for ERT and IBRT [5-8].

Acute toxicity due to pelvic radiotherapy has not been reported well in the litrature. Most studies were retrospective reviews which did not provide enough information about toxicity, especially grade 1 and 2 acute toxicity, hence they were not mentioned by the patient and required a detailed clinical examination on daily practice. Kapp *et al*. analysed the complications after primary external beam radiation and Ir-192 HDR brachytherapy in 161 patients with carcinoma of the cervix. The acute sequelae rate was 41.6% (9). The most frequent side-effects were diarrhea (63%) followed by nausea (30%) and cystitis. The incidence of late complications were as follows: grade 1-50.9%; grade 2-11% and grade 3-3.7%. Yalman *et al*. reported a 41.5% acute morbidity rate in 771 patients with gynaecologic malignancy, grade 1 and 2 bladder morbidity being the most frequent type [5]. In the present study acute morbidity rates for the genitourinary and gastrointestinal system and skin were 52.3%, 73.2% and 63.5%, respectively, according to the RTOG grading system. Due to the prospective design of this study, a detailed clinical examination and documentation might be the reason for more higher acute toxicity rates when compared with the literature.

Corn and associates evaluated late morbidity in 235 patients who received a median dose of 46.2 Gy ERT to the whole pelvis or ERT combined with IBRT with a vaginal cylinder (median vaginal surface dose was 32.4 Gy). At the end of the fifth year the severe morbidity rate was 5.5% [10]. Barillot *et al*. used the Franco-Italian glossary to determine the morbidity rate in 642 patients treated with radiotherapy alone for carcinoma of an intact uterine cervix [11]. The total morbidity rate was 51%. The five-year actuarial toxicity rate per grade was: G1 - 42%; G2 - 23.5%; G3 - 10%; G4 - 3%. The gynaecological tract (31%) and rectum (21.5%) were the most frequent sites of treatment sequelae and complications followed by the pelvic soft tissues (18%), bladder (13%) and small bowel (4%). In the present study, late complication rates according to the RTOG scale were as follows: 16.8% genitourinary, 20.6% gastrointestinal, 49.7% skin, 29.9% subcutaneus tissue, 51.1% mucosa-vagina, and 47.7% skin The complication rates according to the Franco-Italian glossary were as follows: 35.4% bladder-genitourinary, 29.9% nonspecific abdominal-gastrointestinal, 60.8% uterus-vulva-vagina, 40.1% subcutaneous tissue, and 32.7% rectum. Our experience with the Franco-Italian glossary was quite different from the RTOG rates in terms of late effects.

There is no common language between the RTOG and Franco-Italian scoring system in terms of evaluation and rates of toxicities. However, both scoring systems have different difficulties and incompetence regarding toxicity evaluation. There is no scoring in the RTOG system for an anal fissure as it is a common acute toxicity in our experience. Additionally RTOG late toxicity scoring for the vagina is not detailed as demanded regarding vaginal stenosis and telangiectasias. Although RTOG defined severe telangiectasia as a grade 3, in our experience multiple telangiectasias are not as severe as grade 3. Ultimately, asymptomatic telangiectasias scoring as Grade 3 would cause a false-positive increase in grade 3 vaginal toxicity. RTOG late urinary system toxicity scoring has limitations regarding urinary incontinance, cyctocele and asymptomatic leukocyturia. Although, the Franco-Italian scoring system is more detailed compared to RTOG, no definition of acute and late toxicity might cause an underestimation of acute toxicity in daily practice. As a result of the present study, we concluded that a standard and a well-defined user-friendly objective scoring system is needed to define and predict the morbidity rate more properly.

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